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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/147,693 02/17/99 LUBITZ

W P564-9005

EXAMINER

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ART UNIT	PAPER NUMBER
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1636

19

DATE MAILED:

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No. 09/147,693	Applicant(s) Lubitz et al.
Examiner WILLIAM SANDALS	Art Unit 1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on Jul 12, 2001

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) Claim(s) 38-76 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) 49 is/are allowed.

6) Claim(s) 38-48 and 50-76 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are objected to by the Examiner.

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) All b) Some* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) Notice of References Cited (PTO-892) 18) Interview Summary (PTO-413) Paper No(s). _____

16) Notice of Draftsperson's Patent Drawing Review (PTO-948) 19) Notice of Informal Patent Application (PTO-152)

17) Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 20) Other: _____

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DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 12, 2001 has been entered.

Response to Arguments

2. The amendment to claim 38 presented in Paper No. 14, filed May 10, 2001 has been considered, and has prompted new grounds for rejection below.

Claim Objections

3. Claim 52 is objected to because of the following informalities: Claim 52 depends from claim 53. A dependent claim must depend upon a preceding claim, and may not depend upon a claim which follows. Appropriate correction is required.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

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Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 49 is rejected based upon the fact that the claim reads on a naturally occurring sequence. Adding “isolated” before “lambda OR” would cure this defect.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 38 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 38 has been amended to recite “non-naturally occurring” at line 11. This constitutes new matter. There is no literal or inferred support in the specification for the term. Paper No. 14 points to page 5, and to pages 6-7 for support for this amendment, however, a reading of the cited pages provides no terms which provide a basis for the term “non-naturally occurring”. Rather, the passages cited describe a mutated operator sequence, and two well known methods for achieving a mutated operator sequence. This does not provide any support for a term which has the meaning of “non-naturally occurring” as it is used in claim 38.

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7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 38 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 38 recites the term “non-naturally occurring”. “Non-naturally occurring” is not defined in the specification or claims. Without proper guidance as to the meaning of the term, one of ordinary skill in the art would not know the metes and bounds of the claim.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. Claims 46-48, 50-62, 66-70 and 73-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. in view of Eliason et al., Pakula et al., Benson et al., US Pat No. 4,634,678 and US Pat No. 5,576,190.

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This rejection is maintained for reasons of record set forth in the Office Action mailed January 12, 2001 and the rejection is repeated below. Arguments filed in Paper No. 14 have been fully considered but they are not deemed to be persuasive.

The claims are drawn to a method for selecting mutated O_R or O_L operator DNA sequences from lambdoid phages which have different thermostability compared to wild-type sequence with regard to binding a repressor wherein the operator DNA sequence is subjected to mutation and selected for different thermostability from the wild type with respect to binding of a repressor. The repressor may be cI857, and the thermostability may be increased from 3-10° or 7-9°. The claims are also drawn to the mutated O_R or O_L operator DNA sequences from lambdoid phages which may be incorporated into a vector, and to a host bacterial cell.

Chen et al. taught (see especially the abstract, introduction, page 86 and the figures) mutated pL or oL operator DNA sequences from lambdoid phages which may be incorporated into a vector, and to a host bacterial cell, where the cI857 repressor was used to control expression by the operator sequences in a temperature dependent manner.

Chen et al. did not teach that the mutated operator sequences had an altered binding affinity for cI857 repressor, nor that the suicide gene was from PhiX174, nor that a mutator strain of bacteria may be used to induce mutations in the operator sequence, nor the specific temperature ranges of changes in the thermostability of the operator binding repressor, nor that the vector was a bacterial chromosomal vector, nor the use of multiple operator sequences.

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Eliason et al. taught (see especially the abstract, the introduction, page 2342-43 and the tables and figures) a method for selecting mutated O_R or O_L operator DNA sequences from lambdoid phages which have different binding compared to wild-type sequence with regard to binding a repressor wherein the operator DNA sequence is subjected to mutation and selected for different binding from the wild type with respect to binding of a repressor. Eliason et al. also taught mutated O_R or O_L operator DNA sequences from lambdoid phages which may be incorporated into a vector, and to a host bacterial cell.

Pakula et al. taught (see especially the abstract, introduction and the discussion) the change in thermal stability of a mutated repressor protein with the lambda operator. Pakula et al. discuss in great detail, the importance of the contact bases in the operator, and the manner in which they interact with the amino acids of the repressor protein. From their discussion, it is clear that the increased thermal stability of the binding of the repressor protein is directly related to the thermodynamics of the molecular interaction between the contact bases of the operator DNA sequence and the contact amino acids of the repressor protein. Pakula et al. taught that one of skill in the art would be able to select mutated sequences in the repressor protein which would have greater binding affinity for the operator sequences and therefore higher thermostability.

Benson et al. taught (see especially the abstract, the introduction, page 26, column 1, and Page 28, column 1) the relative affinity of the lambda repressor protein for the lambda operator sequence, where the operator sequence has been mutated. Benson et al. show that the operator

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sequence was mutated to produce a mutant operator sequence which has greater affinity for the lambda repressor protein than the wild type operator sequence.

US Pat No. 4,634,678 taught (see especially the abstract, summary and the claims) the use of two or more operator sequences which have different affinities for the cI857 repressor in a single construct to produce different affinities for the cI857 repressor.

US Pat No. 5,576,190 taught (see especially the abstract, summary and column 10) the mutation of OL operator sequences to increase the binding affinity of the cI857 repressor protein.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant invention to combine the mutated DNA lambda operator sequences of Chen et al., Eliason et al. or Benson et al. with the increased thermostability of repressor sequences of Pakula et al. since Pakula et al. taught the increased thermostability of the repressor complex was due to changes in the thermodynamic molecular interaction of specific bases and amino acids in the binding site of the operator/repressor pair. US Pat No. 4,634,678 and US Pat No. 5,576,190 each taught the use of a mutated operator sequence to increase the affinity of the repressor for the operator sequence. Eliason et al. taught the changes in the operator sequence would affect the thermodynamic stability of the interaction of the operator/repressor complex. Since cI857 is a known mutant repressor of the lambda operator, and mutations of the sequence of the cI857 would also be affected by the same thermodynamic laws which apply to the repressor/operator complexes of Chen et al., Eliason et al., US Pat No. 4,634,678, US Pat No. 5,576,190 and Pakula et al., it would have also been obvious to practice the invention with cI857.

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One of ordinary skill in the art would have been motivated at the time of filing of the instant invention to combine the mutated DNA lambda operator sequences of combine the mutated DNA lambda operator sequences of Chen et al., Eliason et al. or Benson et al. with the increased thermostability of operator/repressor binding of Pakula et al. since Pakula et al. taught in the abstract that "two suppressor substitutions increase the thermal stability of Cro by 12° C to 14° C.", and in the introduction, "two substitutions that dramatically increase the thermal stability" of the repressor complex was due to changes in the thermodynamic molecular interaction of specific bases and amino acids in the binding site of the operator/repressor pair (see especially figure 4). US Pat No. 4,634,678 and US Pat No. 5,576,190 each taught the use of a mutated operator sequence to increase the affinity of the repressor for the operator sequence. Eliason et al. taught in the abstract and in the introduction that the changes in the operator sequence would affect the thermodynamic stability of the interaction of the operator/repressor complex. Since cI857 is a known repressor mutant of the lambda operator, and mutations of the sequence of the cI857 would also be affected by the same thermodynamic laws which apply to the repressor/operator complexes of Eliason et al. and Pakula et al., it would have also been obvious to practice the invention with cI857. Benson et al. taught at page 28, "[f]rom our analysis of symmetric operators, we can rank changes in the natural operators as being severely detrimental, mildly detrimental, neutral, or beneficial for the binding of repressor". The teachings of Eliason et al. that mutation of the operator causes a change in the binding temperature of the lambda repressor to the lambda operator is confirmed and strengthened by the

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teachings of Benson et al. on the effects of mutation of the lambda operator in the binding affinity of the lambda repressor with the lambda operator. This makes it obvious to one of skill in the art that mutations in the lambda operator sequence would affect the temperature of activation of the lambda repressor by changing the affinity of the lambda repressor for the lambda operator. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Chen et al. in view of Eliason et al., Pakula et al., Benson et al., US Pat No. 4,634,678 and US Pat No. 5,576,190.

Response to Arguments

12. Arguments set forth in Paper No. 10 assert that even though Chen et al. taught mutations to the pL and oL promoter regions in an assay system which employed the cI857 repressor, Chen et al. does not teach that the mutant operator regions actually had an altered affinity for the cI857 repressor, and therefore should not be used as a reference in the rejection. Chen et al. did in fact teach that the pL and oL operator regions were mutated, and that the mutant operator regions did have an altered expression of the reporter gene. Chen et al. did not investigate the affinity of the cI857 repressor for the mutated operator regions, and therefore is silent with respect to the affinity of the cI857 repressor for the mutated operator regions. This lack of attention to the affinity of the mutated operator sequences to the cI857 repressor in Chen et al. is clarified by the remaining references of the rejection. The argument is therefore not found convincing.

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13. Arguments set forth in Paper No. 10 assert that Eliason et al. does not teach that the thermostability of the mutated operator sequences is increased. True. However, Eliason et al. do show that mutated operator sequences have an altered affinity for the repressor.

14. Arguments set forth in Paper No. 10 assert that Pakula et al. teach a mutated repressor, not the mutated operator of the instant claims. This is true. However, Pakula et al. taught the molecular mechanism of the binding of a repressor to an operator, making abundantly clear the fact that the binding of the repressor to the operator follows predictable and well known thermodynamic principals which may be affected by a mutated operator sequence. The Benson et al. reference is used to make obvious the well known fact that the teachings of Pakula et al. on the thermodynamic principals of binding of a repressor to an operator sequence definitely apply to the mutation of the operator sequence of the instant claimed invention.

15. Arguments set forth in Paper No. 10 assert that the teachings of US Pat No. 4,634,678 and US Pat No. 5,576,190 do not teach that a mutated operator sequence has higher affinity for the cI857 repressor. Contrary to this assertion US Pat No. 5,576,190 at column 10, lines 39-56 recites "transcriptional activating sequences of psynC and psyn3 contain a -10 consensus sequence and alteration in the first repressor binding regions....This alteration results in enhanced transcriptional activating activity with a minimum effect on repressor binding and repressibility. pHDM159 contains a change that increases the binding affinity for the cI857 repressor. Thus, the present invention includes a variety of modified bacteriophage lambda pL promoter-operator regions which provide for increased vector stability while providing regulated expression of an

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operably linked gene". Thus, US Pat No. 5,576,190 does teach the increased affinity of a mutated operator for a cl857 repressor, and US Pat No. 4,634,678 teaches (see the summary and Table I) the application of oR and oL operators in a single construct, as well as a mutated operator which binds cl857 in the summary, especially at Table I of the summary as stated in the rejection. These limitations are further elaborated at sections 5.7.1-5.10.3 of US Pat No. 4,634,678.

16. Claims 38-48, 50-62, 66-70 and 73-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. in view of Eliason et al., Pakula et al., Benson et al., US Pat No. 4,634,678 and US Pat No. 5,576,190. as applied to claim 38-42, 44-48, 50-62, 66-70 and 73-76 above, and further in view of US Pat No. 5,811,093.

This rejection is maintained for reasons of record set forth in the Office Action mailed January 12, 2001 and the rejection is repeated below. Arguments filed in Paper No. 14 have been fully considered but they are not deemed to be persuasive.

The claims are drawn as described above and to method of use of a mutator bacterial strain to carry out the mutagenesis of the lambda operator sequence.

US Pat No. 5,811,093 taught (see especially the abstract, summary and columns 18-19) a mutator bacterial strain used for the well known mutation of a desired sequence of phage DNA.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant claimed invention to use a mutator strain of bacteria such as the mutator strain of US Pat

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No. 5,811,093 because of the well known use of such a strain of bacteria to produce mutations in a selected DNA sequence such as the instant claimed lambda operator sequence.

One of ordinary skill in the art would have been motivated at the time of filing of the instant claimed invention to use a mutator strain of bacteria such as the mutator strain of US Pat No. 5,811,093 because it was well known to those of ordinary skill in the art that a mutator strain of bacteria would produce the desired mutations in a selected sequence of DNA such as the instant claimed lambda operator sequence. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of unpatentable over Chen et al. with Eliason et al., Pakula et al., Benson et al., US Pat No. 4,634,678 and US Pat No. 5,576,190. and further with US Pat No. 5,811,093.

17.

Response to Arguments

Arguments set forth in Paper No. 8 assert that Eliason et al. does not teach the increase in thermostability of the cl857 repressor for the mutated operator sequences. Eliason et al. taught that the mutated operator sequences have a higher affinity for the cl857 repressor. Pakula et al. taught the thermodynamics of the interaction of a repressor with mutated operator sequences. Pakula et al. make it very clear that an increase in affinity of the repressor for the operator sequences will also increase the thermostability of the repressor as it binds to the mutated operator sequences.

Arguments set forth in Paper No. 8 assert that Pakula et al. and Benson et al. do not teach the cl857 repressor. The teachings of Pakula et al. and Benson et al. are used to demonstrate

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features of the invention which are clearly relevant to the teachings of the primary reference, and make obvious the instant invention.

18. Arguments set forth in Paper No. 14, filed May 10, 2001 assert that the Pakula et al. reference has been misinterpreted. It is asserted that, rather than discussing the thermostability of the operator/repressor complex, Pakula et al. discuss the thermostability of the Cro repressor. The first line of the Final Office Action rejection refers to the fact that the teachings of Pakula et al. are directed to the thermostability of the repressor protein. Pakula et al. teaches important general knowledge of those of ordinary skill in the art regarding the basic thermodynamics of molecular binding, and its general results on the thermostability of a DNA/repressor binding complex. Repressor protein binding to the operator DNA sequences must follow the laws of thermodynamics that are well set forth in Pakula et al. Pakula et al. does teach that the binding affinity of a repressor protein to lambda operator sequences is affected by changes in the lambda operator DNA sequence. Pakula et al. teaches that the thermostability of the operator/DNA complex is altered by changes in the binding affinity. This is well known information regarding the thermodynamics of protein/DNA binding. Stronger binding affinity results in higher thermostability of the complex and weaker binding affinity results in lower thermostability. The lesson taught by Pakula et al. is basic to the understanding of the physical principles of molecular interaction.

19. Arguments set forth in Paper No. 14 assert that Benson et al. did not teach mutated operator sequences having increased thermostability. Referring to the discussion above, Benson

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taught that repressor bound to mutated operator DNA sequences with different affinities with respect to the changes in the DNA sequence. The different binding affinities of the mutated operator sequences must result in different thermal stabilities of the repressor/operator complex.

The fact that Benson et al. does not mention thermostability is irrelevant to the basic physical principles which underlie the binding affinities. Requiring Benson et al. to specifically mention this fact is not necessary to make the point, since the physical principals must apply in all cases.

20. Arguments set forth in Paper No. 14 assert that US 5,576,190 taught “tighter regulation” at column 7, lines 11-20. As pointed out in the Final Office Action, column 10, (lines 48-49) “pHDM159 contains a change that increases the binding affinity for the cI857 repressor”. As above, changes in the binding affinity must also affect the thermostability of the complex.

21. Arguments set forth in Paper No. 14 assert that by amending claim 38 to recite “non-naturally occurring mutagenesis”, this distinguishes the claim from Chen et al. The argument set forth in Paper 14 acknowledges at page 7 that US 5,811,093 provides well known teachings on the use of a mutator bacterial strain to one of ordinary skill in the art for the purposes of mutating the instant operator sequences. This is sufficient motivation to combine the references and would lead one of ordinary skill in the art to mutate the mutated sequences of Chen et al. to provide the mutated operator sequences of the instant claimed invention.

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22. Claims 38-48 and 50-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. with Eliason et al., Pakula et al., Benson et al., US Pat No. 4,634,678 and US Pat No. 5,576,190 as applied to claims 38-42, 44-48, 50-62, 66-70 and 73-76 above, and further in view of Szostak et al.

This rejection is maintained for reasons of record set forth in the Office Action mailed January 12, 2001 and the rejection is repeated below. Arguments filed in Paper No. 14 have been fully considered but they are not deemed to be persuasive.

The claims are as described in the rejection above and to a vaccine composition comprising the bacterial cell and bacterial cell ghosts produced by transfecting bacterial cells with the above claimed compositions and methods.

Chen et al. with Eliason et al., Pakula et al., Benson et al., US Pat No. 4,634,678 and US Pat No. 5,576,190 did not teach the vaccine composition comprising the bacterial cell and bacterial cell ghosts produced by transfecting bacterial cells with the above claimed compositions and methods.

Szostak et al. taught (see especially the abstract, materials and methods and the figures) vaccines made by transfecting bacterial cells with the above claimed compositions and methods.

It would have been obvious to one of ordinary skill in the art at the time of filing the instant claimed invention to combine the composition comprising the transfecting of bacterial cells with the above claimed compositions and methods of Chen et al. with Eliason et al., Pakula et al., Benson et al., US Pat No. 4,634,678 and US Pat No. 5,576,190 with the vaccine

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composition comprising the bacterial cell and bacterial cell ghosts of Szostak et al. because Szostak et al. used the bacterial cells transfected with the above claimed compositions and methods to make vaccines with bacteria and bacterial ghosts according the instant claimed invention. Szostak et al. state at page 424 “[g]eneration of humoral and cellular immune responses by bacterial ghosts carrying RT-specific fusion proteins in the cell envelope indicates that this approach of immunostimulation by carrier cells and targeting antigens might be useful in the development of candidate vaccines. As the immune response is directed against the carrier and the membrane, targeted fusion protein combination vaccines can be envisaged.” These comments make it clear, combined with the success of producing an immunized animal with the bacterial cell ghosts, that it would have been obvious to combine the teachings of the vectors of Chen et al. with Eliason et al., Pakula et al., Benson et al., US Pat No. 4,634,678 and US Pat No. 5,576,190 and Szostak et al to produce the instant claimed vaccine compositions. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Chen et al. with Eliason et al., Pakula et al., Benson et al., US Pat No. 4,634,678 and US Pat No. 5,576,190 and Szostak et al.

Conclusion

23. Certain papers related to this application are *welcomed* to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or

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applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.
Examiner
August 20, 2001



TERRY MCKELVEY
PRIMARY EXAMINER